IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Paz Einat, et al.

U.S. Serial No. : 10/561,005

Filed : as §371 national stage of PCT International Application No. PCT/IL2004/000515

For : METHODS FOR CLONING NUCLEIC ACIDS IN A DESIRED ORIENTATION

1185 Avenue of the Americas
New York, New York 10036
May 24, 2006

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO MARCH 24, 2006 NOTIFICATION TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

This Amendment is submitted in response to the March 24, 2006 Notification to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures issued by the United States Patent and Trademark Office in connection with the above-identified application. The March 24, 2006 Notification, a copy of which is attached hereto as **Exhibit A**, provides two (2) months for filing a response. Therefore, a response to the March 24, 2006 Notification is due May 24, 2006. Accordingly, this Amendment is being timely filed.

Amendments to the Specification begin on page 2 of this paper.

A substitute **Sequence Listing** is referred to on page 6 of this paper and attached hereto as **Exhibit B**.

Remarks begin on page 7 of this paper.
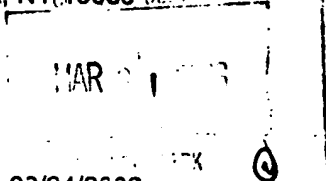
2094| 69626-A-PCT-US

JPW

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/561,005	Paz Einat	69626-A-PCT-US/JPW/JW

INTERNATIONAL APPLICATION NO.
PCT/IL04/00515

I.A. FILING DATE	PRIORITY DATE
06/15/2004	06/16/2003

23432
COOPER & DUNHAM, LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

MAR

Date Mailed: 03/24/2006

2mo -5|24|06
3mo -6|24|04
4mo -7|24|04
5mo -8|24|06
6mo -9|24|06
7mo -10|24|06

CONFIRMATION NO. 9425
371 FORMALITIES LETTER

OC000000018387668

NOTIFICATION TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to file the items indicated below to avoid abandonment. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

- A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing." Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to 37 CFR 1.821-1.825 requirements, please contact:

- **For Rules Interpretation, call (571) 272-0951**
- **For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.**
- **Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov**

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

A copy of this notice MUST be returned with the response.

DEBORAH D WILLIAMS

Telephone: (703) 308-9140 EXT 205

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PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/561,005	PCT/IL04/00515	69626-A-PCT-US/JPW/JW

FORM PCT/DO/EO/922 (371 Formalities Notice)

RAW SEQUENCE LISTING ERROR REPORT

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: 10/561,005
Source: IFWP
Date Processed by STIC: 12/30/05

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.
PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:
1) INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,
2) TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY
FOR CRF SUBMISSION AND PATENTIN SOFTWARE QUESTIONS, PLEASE CONTACT MARK SPENCER, TELEPHONE: 571-272-2510; FAX: 571-273-0221

TO REDUCE ERRORED SEQUENCE LISTINGS, PLEASE USE THE **CHECKER VERSION 4.2.2 PROGRAM**, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW FOR ADDRESS:
http://www.uspto.gov/web/offices/pac/checker/chkrnote.htm

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there i a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail.
Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom.
Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm> , EFS Submission User Manual - ePAVE)
2. U.S. Postal Service: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450)
3. Hand Carry, Federal Express, United Parcel Service, or other delivery service (EFFECTIVE 01/14/05): U.S. Patent and Trademark Office. Mail Stop Sequence, Customer Window, Randolph Building. 401 Dulany Stree Alexandria, VA 22314

Revised 01/24/05

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2 ____ Invalid Line Length — The rules require that a line not exceed 72 characters in length. This includes white spaces.

3 ____ Misaligned Amino — The numbering under each 5th amino acid is misaligned. Do not use tab codes between numbers; use space characters, instead.
Numbering

4 ____ Non-ASCII — The submitted file was not saved in ASCII(DOS) text, as required by the Sequence Rules. Please ensure your subsequent submission is saved in ASCII text.

5 ____ Variable Length — Sequence(s) ____ contain n's or Xaa's representing more than one residue. Per Sequence Rules, each n or Xaa can only represent a single residue. Please present the maximum number of each residue having variable length and indicate in the <220>-<223> section that some may be missing.

6 ____ PatentIn 2.0 — A "bug" in PatentIn version 2.0 has caused the <220>-<223> section to be missing from amino acid
"bug" sequences(s) _____. Normally, PatentIn would automatically generate this section from the previously coded nucleic acid sequence. Please manually copy the relevant <220>-<223> section to the subsequent amino acid sequence. This applies to the mandatory <220>-<223> sections for Artificial or Unknown sequences.

7 ____ Skipped Sequences — Sequence(s) _____ missing. If intentional, please insert the following lines for each skipped sequence:
(OLD RULES) (2) INFORMATION FOR SEQ ID NO:X: (insert SEQ ID NO where "X" is shown)
(I) SEQUENCE CHARACTERISTICS: (Do not insert any subheadings under this heading)
(xi) SEQUENCE DESCRIPTION:SEQ ID NO:X: (insert SEQ ID NO where "X" is shown)
This sequence is intentionally skipped

Please also adjust the "(ii) NUMBER OF SEQUENCES:" response to include the skipped sequences.

8 ____ Skipped Sequences — Sequence(s) _____ missing. If intentional, please insert the following lines for each skipped sequence.
(NEW RULES) <210> sequence id number
<400> sequence id number
000

9 ____ Use of n's or Xaa's — Use of n's and/or Xaa's have been detected in the Sequence Listing.
(NEW RULES) Per 1.823 of Sequence Rules, use of <220>-<223> is MANDATORY if n's or Xaa's are present. In <220> to <223> section, please explain location of n or Xaa, and which residue n or Xaa represents.

10 ____ Invalid <213> — Per 1.823 of Sequence Rules, the only valid <213> responses are: Unknown, Artificial Sequence, or
Response scientific name (Genus/species). <220>-<223> section is required when <213> response is Unknown or is Artificial Sequence

11 ____ Use of <220> — Sequence(s) _____ missing the <220> "Feature" and associated numeric identifiers and responses. Use of <220> to <223> is MANDATORY if <213> "Organism" response is "Artificial Sequence" or "Unknown." Please explain source of genetic material in <220> to <223> section. (See "Federal Register," 06/01/1998, Vol. 63, No. 104, pp. 29631-32) (Sec. 1.823 of Sequence Rules)

12 ____ PatentIn 2.0 — Please do not use "Copy to Disk" function of PatentIn version 2.0. This causes a corrupted file,
"bug" resulting in missing mandatory numeric identifiers and responses (as indicated on raw sequence listing). Instead, please use "File Manager" or any other manual means to copy file to floppy disk.

13 ____ Misuse of n/Xaa — "n" can only represent a single nucleotide; "Xaa" can only represent a single amino acid

AMC – Biotechnology Systems Branch – 09/09/2003

RAW SEQUENCE LISTING   DATE: 12/30/2005
PATENT APPLICATION: US/10/561,005   TIME: 09:45:20

Input Set : A:\103-PCT1-US1.ST25.txt
Output Set: N:\CRF4\12302005\J561005.raw

3 <110> APPLICANT: Paz Einat et al./Quark Biotech, Inc.
5 <120> TITLE OF INVENTION: Methods for cloning nucleic acids in a desired orientation
7 <130> FILE REFERENCE: 103/PCT1-US1
9 <140> CURRENT APPLICATION NUMBER: US/10/561,005
10 <141> CURRENT FILING DATE: 2005-12-16
12 <150> PRIOR APPLICATION NUMBER: PCT/IL 2004/000515
13 <151> PRIOR FILING DATE: 2004-06-15
15 <150> PRIOR APPLICATION NUMBER: 60/479,224
16 <151> PRIOR FILING DATE: 2003-06-16
18 <160> NUMBER OF SEQ ID NOS: 14
20 <170> SOFTWARE: PatentIn version 3.2
22 <210> SEQ ID NO: 1
23 <211> LENGTH: 24
24 <212> TYPE: DNA
25 <213> ORGANISM: Artificial
27 <220> FEATURE:
28 <223> OTHER INFORMATION: Artificial DNA
31 <220> FEATURE:
32 <221> NAME/KEY: misc_feature
33 <222> LOCATION: (21)..(24)
34 <223> OTHER INFORMATION: "n"=nucleotide A, T, G or C
36 <400> SEQUENCE: 1
37 gccattaagg ccaccatgcc nnnn
40 <210> SEQ ID NO: 2
41 <211> LENGTH: 41
42 <212> TYPE: DNA
43 <213> ORGANISM: Artificial
45 <220> FEATURE:
46 <223> OTHER INFORMATION: Artificial DNA
48 <400> SEQUENCE: 2
49 catggtggcc ttaatggcca ctacgaccgt tcgggtggta c
52 <210> SEQ ID NO: 3
53 <211> LENGTH: 24
54 <212> TYPE: DNA
55 <213> ORGANISM: Artificial
57 <220> FEATURE:
58 <223> OTHER INFORMATION: Artificial DNA
61 <220> FEATURE:
62 <221> NAME/KEY: misc_feature
63 <222> LOCATION: (21)..(24)
64 <223> OTHER INFORMATION: n=nucleotide A, T, G or C
66 <400> SEQUENCE: 3
67 gccattaagg ccaccatgcc nnnn

Handwritten annotations: pp 1-4; Does Not Comply / Corrected Diskette Needed; insufficient explanation (give source of genetic material) (see item 11 on Euro summary sheet); 24; 41; 24; OK

```
70 <210> SEQ ID NO: 4
71 <211> LENGTH: 41
72 <212> TYPE: DNA
73 <213> ORGANISM: Artificial
75 <220> FEATURE:
76 <223> OTHER INFORMATION: Artificial DNA
78 <400> SEQUENCE: 4                                              41
79 catggtgggc ttgccagcat caccggtaat tccggtggta c
82 <210> SEQ ID NO: 5
83 <211> LENGTH: 21
84 <212> TYPE: DNA
85 <213> ORGANISM: Artificial
87 <220> FEATURE:
88 <223> OTHER INFORMATION: Artificial DNA
91 <220> FEATURE:
92 <221> NAME/KEY: misc_feature
93 <222> LOCATION: (1)..(4)
94 <223> OTHER INFORMATION: n = nucleotide A, T, G or C
96 <400> SEQUENCE: 5                                              21
97 nnnnggtgag tgactgaggc c
100 <210> SEQ ID NO: 6
101 <211> LENGTH: 44
102 <212> TYPE: DNA
103 <213> ORGANISM: Artificial
105 <220> FEATURE:
106 <223> OTHER INFORMATION: Artificial DNA
108 <400> SEQUENCE: 6                                              44
109 cgaggagcga ccgactcgat ggccgaggcg gcctcagtca ctca
112 <210> SEQ ID NO: 7
113 <211> LENGTH: 21
114 <212> TYPE: DNA
115 <213> ORGANISM: Artificial
117 <220> FEATURE:
118 <223> OTHER INFORMATION: Artificial DNA
121 <220> FEATURE:
122 <221> NAME/KEY: misc_feature
123 <222> LOCATION: (1)..(4)
124 <223> OTHER INFORMATION: n = nucleotide A, T, G or C
126 <400> SEQUENCE: 7                                              21
127 nnnnggtgag tgactgaggc c
130 <210> SEQ ID NO: 8
131 <211> LENGTH: 44
132 <212> TYPE: DNA
133 <213> ORGANISM: Artificial
135 <220> FEATURE:
136 <223> OTHER INFORMATION: Artificial DNA
138 <400> SEQUENCE: 8                                              44
139 actcactgac tccggcggag ccggtagctc agccagcgag gagc
142 <210> SEQ ID NO: 9
```

143 <211> LENGTH: 21
144 <212> TYPE: DNA
145 <213> ORGANISM: Artificial
147 <220> FEATURE:
148 <223> OTHER INFORMATION: Artificial DNA

21

150 <400> SEQUENCE: 9
151 gtaccacccg aacggtcgta g

154 <210> SEQ ID NO: 10
155 <211> LENGTH: 13
156 <212> TYPE: DNA
157 <213> ORGANISM: Artificial
159 <220> FEATURE:
160 <223> OTHER INFORMATION: Artificial DNA
163 <220> FEATURE:
164 <221> NAME/KEY: misc_feature
165 <222> LOCATION: (5)..(9)
166 <223> OTHER INFORMATION: n = nucleotide A, T, G or C

13

168 <400> SEQUENCE: 10
169 ggccnnnnng gcc

172 <210> SEQ ID NO: 11
173 <211> LENGTH: 13
174 <212> TYPE: DNA
175 <213> ORGANISM: Artificial
177 <220> FEATURE:
178 <223> OTHER INFORMATION: Artificial DNA
181 <220> FEATURE:
182 <221> NAME/KEY: misc_feature
183 <222> LOCATION: (5)..(9)
184 <223> OTHER INFORMATION: n = nucleotide A, T, G or C

13

186 <400> SEQUENCE: 11
187 ccggnnnnnc cgg

190 <210> SEQ ID NO: 12
191 <211> LENGTH: 5
192 <212> TYPE: DNA
193 <213> ORGANISM: Artificial
195 <220> FEATURE:
196 <223> OTHER INFORMATION: Artificial DNA

5

198 <400> SEQUENCE: 12
199 aggcc

202 <210> SEQ ID NO: 13
203 <211> LENGTH: 5
204 <212> TYPE: DNA
205 <213> ORGANISM: Artificial
207 <220> FEATURE:
208 <223> OTHER INFORMATION: Artificial DNA

5

210 <400> SEQUENCE: 13
211 ccggg

214 <210> SEQ ID NO: 14
215 <211> LENGTH: 46

216 <213> TYPE: DNA
217 <21> ORGANISM: Artificial
219 <240> FEATURE
220 <223> OTHER INFORMATION: Artificial DNA
222 <400> SEQUENCE: 14

223 gaattggcca ttaaggcctg caggatccgg ccgcctcggc ctcgag

46

Please note:
use of n and/or Xaa have been corrected in the Sequence Listing. Please review the
sequences relating to ensure that the corresponding explanation is presented in the <220>
to <223> fields of each sequence which presents at least one n or Xaa.

Seq#:1; N Pos. 21,22,23,24
Seq#:3; N Pos. 21,22,23,24
Seq#:5; N Pos. 1,2,3,4
Seq#:7; N Pos. 1,2,3,4
Seq#:10; N Pos. 5,6,7,8,9
Seq#:11; N Pos. 5,6,7,8,9

Invalid <213> Response:
Use of "Artificial" only as "<213> Organism" response is incomplete,
per 1.823(b) of New Sequence Rules. Valid response is Artificial Sequence.

Seq#:1,2,3,4,5,6,7,8,9,10,11,12,13,14

L:9 M:
L:10 M:
L:37 M:341 W:
L:67 M:341 W: "n" or "Xaa" used, for SEQ ID#:5 after pos:0
L:97 M:341 W: "n" or "Xaa" used, for SEQ ID#:7 after pos:0
L:127 M:341 W: "n" or "Xaa" used, for SEQ ID#:10 after pos:0
L:169 M:341 W: "n" or "Xaa" used, for SEQ ID#:11 after pos:0
L:187 M:341 W: